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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 02/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/603,385	ZHANG, FEN	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 June 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

An amendment was received and entered on 11/26/04.

Claims 1-20, and the elected invention of "growth factors" and "amniotic membrane" are under consideration in this Office Action.

Priority

Priority is claimed in the first line of the specification to provisional application 60/391,550, filed 6/24/2002. The effective filing date of the application is considered to be 6/24/2002.

Specification

Applicant's amendment to delete citations 28-36, that do not correspond to any reference, overcomes the previous objection to the specification.

Rejections Withdrawn

The rejection of claims 1-15 for indefiniteness because the recited method steps are not concordant with the purpose set forth in the preamble is withdrawn. After further consideration, the claims are considered to be very broad, rather than indefinite.

The rejection of claims 12 and 13 for indefiniteness because they recited "the function of a membrane" without proper antecedent basis is overcome by Applicant's amendment.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9 and 16-20 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 9 and 16-20 are indefinite because it is unclear what are the metes and bounds of "a nutrient poor environment found on the skin". The specification does not define "nutrient-poor environment" in the context of the skin, stating only that "the dermal surface is generally considered to be a nutrient-poor environment" (see paragraph 160). The term "poor" in this context is a relative term that modifies the parameter of nutrient abundance. Because "poor" is not defined by the claims, and the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Response to Arguments

Applicant's arguments filed 11/26/04 have been fully considered but they are not persuasive. Applicant argues at pages 6 and 7 of the response that a skilled artisan would understand the phrase in question. This argument is unpersuasive because it lacks logical or evidentiary support.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 1-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods and compositions for delivering a growth factor to a wound in the skin of a patient by administering to the wound site amniotic epithelial cells that secrete the growth factor, does not reasonably provide enablement for obtaining desired effects other than wound healing, for delivering molecules other than growth factors, or for methods of delivering molecules to sites other than the site of cell administration. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to methods and compositions for delivering a molecule to a patient comprising administering to the patient amniotic epithelial cells, wherein said cells are capable of delivering the molecule. The specification defines the term patient as the recipient of the molecule to be delivered regardless of the purpose of such delivery (detailed description paragraph 74), so the claims are not limited to medical treatment. The claims embrace methods and compositions intended to provide desired effects such as therapeutic, cosmetic, prophylactic, and diagnostic effects. While no pending claim requires the use of engineered epithelial cells to deliver products encoded by exogenous genes, this use is embraced by the instant claims, and the specification is largely directed to this method. The recited therapeutic, cosmetic, and

prophylactic effects are not limited in breadth. As a result they embrace effects as diverse as the treatment and cure of HIV, glioblastoma, cystic fibrosis, and wound healing. There is no recited nexus between the site of cell administration and the site of molecule delivery, so the claims embrace systemic molecule delivery, as well as molecule delivery to specific target organs such as the brain, kidneys, and lungs through application to the skin. Additionally, the claims are not limited to the delivery of peptides or polypeptides, but embrace the delivery of any molecule without limitation to any site without limitation for the purpose of eliciting any desired effect.

The specification provides no working example of the delivery of any molecule to a patient through the use of the amniotic epithelial cells. No guidance is presented as to how to deliver any type of molecule other than a secretable gene product. No guidance is presented with regard to how many amniotic epithelial cells must be transfected with what type of expression construct to achieve the appropriate level of expression of any specific gene product for any specific desired effect. Instead the specification teaches a working example in which an amniotic membrane is stripped of its epithelium, reconstituted with Madin-Darby Canine Kidney (MDCK) cells that stably express PDGF-beta, and applied to a rabbit chronic wound model. Accelerated healing is reported. However, as noted above, the claims are in no way limited to wound healing, but embrace delivery of any molecule to any site of any patient for the diagnosis or treatment of any cosmetic or medical condition. The specification provides no guidance at all regarding how much expression is required of any of the 52 species of molecules recited in claim 7 for any therapeutic, cosmetic, or prophylactic purpose, e.g. for the

treatment of HIV or glioblastoma. As noted above, the specification also fails to provide any guidance as to how to use the claimed invention to delivery any molecule other than a polypeptide or a peptide.

Claim embodiments relating to obtaining therapeutic, cosmetic, and prophylactic effects by delivery of genetically modified cells that express a desired polypeptide or peptide are not adequately enabled due to a lack of guidance. This art was recognized as highly unpredictable at the time of filing, and the specification fails to provide the guidance that is missing from the prior art. At the time the invention was made, successful implementation of gene therapy protocols was not routinely obtainable by those skilled in the art. Verma et al (Nature 389: 239-242, 1997) teach that "there is still no single outcome that we can point to as a success story (p. 239, col 1). The authors state further, "Thus far, the problem has been the inability to deliver genes efficiently and to obtain sustained expression" (p.239, col. 3). With specific regard to ex vivo therapy using retroviral vectors, Verma taught that expression of transgenes was shut off within five to seven days, even in animals lacking a functional immune system. Verma also points out that the search for an appropriate enhancer-promoter combination is a case of trial and error for each given type of cell. See page 240, column 2, lines 10-1, and sentence bridging columns 2 and 3. Anderson (Nature 392:25-30, 1998) confirms the unpredictable state of the art, stating that "there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease" (p. 25, col. 1) and concluding, "Several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after

genes are delivered" (p.30). More recently, Romano et al (2000) reviewed the general state of gene therapy, and found that the problems relating to gene delivery and expression discussed above persisted. See entire document, especially, last sentence of abstract; last sentence of column 1 on page 20 to column 2, line 6; page 21, column 1, lines 1-9 and 18-21; sentence bridging columns 1 and 2 on page 21; and first sentence of last paragraph on page 21.

However, the prior art teaches that wound healing may be facilitated by the delivery to a wound of expression vectors encoding growth factors. See e.g. US Patent 5962427, claims 1-14, and especially claims 6-11. Furthermore, the prior art teaches that epithelial cells may be transfected with expression vectors encoding growth factors, applied to a membrane, and administered to a wound to improve healing. For example, Eming (Invest. Dermatol. 105(6): 756-763, 1995) taught that grafts of keratinocyte monolayers retrovirally modified to overexpress PDGF-A aided in tissue regeneration when administered to the skin of immunodeficient (athymic) mice. See abstract, and page 757, column 2, fourth full paragraph. These results were reproduced by Eming et al (Biotech. Bioeng. 52: 15-23, 1996), see abstract and page 19, column 1, first full paragraph, and column 2, first full paragraph. As a result methods of improving wound healing by administration of epithelial cells modified to express growth factors is considered to be enabled.

However, the prior art and specification do not enable the treatment of wounds, or any other therapeutic, prophylactic, cosmetic, or diagnostic effect by delivery of molecules other than growth factors, as there is no guidance whatsoever as to how to

use amniotic epithelial cells to deliver any molecule other than a peptide or polypeptide. The specification also provides no guidance at all regarding treating such diverse diseases as HIV, glioblastoma, or cystic fibrosis with any molecule, although these treatments are embraced within the metes and bounds of the claims. The specification also provides inadequate guidance as to how to improve wound healing with molecules other than growth factors. Wound healing is recognized as a very complex process involving intricate interactions between a variety of cell types, structural proteins, growth factors, and proteinases. (Stadelmann, W.K., et al., Am J Surg 176(Supp 2A):26S-38S, (1998)). Some of the factors involved in wound healing may affect more than one aspect of the process. So, when a therapeutic regime is contemplated for impaired wound healing, the various process involved in wound healing, i.e. inflammation, angiogenesis, mesenchymal cell chemotaxis and proliferation, epithelialization, wound contraction, collagen synthesis, and remodeling, must be critically considered, and an accurate diagnosis of the factors impairing wound healing must be made. See Eming et al (Cells, Tissues, Organs (2002) 172(2): 105-117) page 106, column 2, first full paragraph. The specification provides no guidance as to the appropriate level of expression of any gene product, nor how to obtain and limit expression within such limits. For example, although the specification suggests the use of anti-inflammatory proteins, it provides no guidance as to how much expression of any anti-inflammatory protein is therapeutic. This is a critical omission in view of the fact that it is recognized in the specification and the prior art that inflammation is a normal part of wound healing. Indeed, Eming (2002) taught that impairment of inflammation could cause inadequate

angiogenesis, mesenchymal cell chemotaxis and proliferation, epithelialization, wound contraction, collagen synthesis, and remodeling. It follows that overexpression of anti-inflammatories could actually impede wound healing.

The high degree of unpredictability associated with the claimed method underscores the need to provide teachings in the specification that would provide the artisan with specific treatment regimens that achieve a therapeutic, cosmetic, diagnostic, or prognostic effect. However, the specification does not provide such guidance and fails to provide any correlation between vectors, cells comprising vectors, dosage amounts, therapeutic genes other than growth factor genes, and any specific disease or condition treatable by the nucleic acids or cells comprising such as disclosed in the instant specification. Without such guidance in the specification and the lack of correlative working examples, the claims would require an undue amount of experimentation without a predictable degree of success on the part of the skilled artisan.

Response to Arguments

Applicant's arguments filed 11/26/04 have been fully considered but they are not persuasive. Applicant argues at page 7 of the response that a skilled artisan could perform the claimed method without undue experimentation understand the phrase in question. This argument is unpersuasive because it lacks logical or evidentiary support. Applicant states that they "do not fully appreciate the nexus of the Examiner's reasoning to the subject invention as recited." To clarify:

The claimed invention is drawn to methods and compositions for delivering a molecule to a patient comprising administering to the patient amniotic epithelial cells, wherein said cells are capable of delivering the molecule. The bulk of the specification is devoted to methods in which the cell is genetically modified to express the delivered molecule. Although the claims do not require this, it is clearly within the intended scope of the claims. The claims embrace methods and compositions intended to provide an unlimited breadth of therapeutic, cosmetic, prophylactic, and diagnostic effects. As a result they embrace effects as diverse as the treatment and cure of HIV, glioblastoma, cystic fibrosis, and wound healing. This breadth is not reasonably enabled for the reasons set forth in the rejection.

The claims recite no nexus between the site of cell administration and the site of molecule delivery. As a result, the claims embrace systemic molecule delivery through application of cells to the skin, as well as molecule delivery to specific target organs such as the brain, kidneys, and lungs. This breadth is not reasonably enabled for the reasons set forth in the rejection.

Additionally, the claims are not limited to the delivery of peptides or polypeptides, but embrace the delivery of any molecule without limitation, to any site without limitation, for the purpose of eliciting any desired effect. This breadth is not reasonably enabled for the reasons set forth in the rejection.

Regarding the more limited scope of the claimed invention that is directed to the treatment of wounds by the application of amniotic epithelial cells that deliver a

molecule, the specification is enabling only for the scope of cells that secrete growth factors, in view of the Wands analysis given above.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-12, and 14-20 stand rejected under 35 U.S.C. 102(b) as being anticipated by Sakuragawa (US Patent 6117676, issued 9/12/00), as evidenced by Uchida et al (J. Neurosci. Res. 62: 585-590, 2000).

This rejection is directed to a generic embodiment of the rejection which does not require amniotic membrane, rather than to the elected embodiment that requires an amniotic membrane.

Sakuragawa taught methods of transfecting human amniotic epithelial cells with adenoviral or plasmid vectors, and disclosed methods of using the cells to treat lysosomal storage diseases by implanting in the subcutis cells encapsulated in a plastic film. See column 3, lines 51-67; column 4, lines 1-16 and 25-35; and column 5, line 25 to column 6, line 17. Inasmuch as the cells of Sakuragawa are composed of molecules, Sakuragawa teaches the delivery of molecules to skin of a patient. Regarding the elected species of molecule to be delivered, i.e. a growth factor, Uchida et al (J.

Neurosci. Res. 62: 585-590, 2000) taught that amniotic epithelial cells were known prior to the time of filing to secrete the growth factor NGF. See abstract.

With regard to claim 12, note that the instant specification does not define the term "synthetic membrane" so it has been given its broadest reasonable interpretation. In this interpretation, the plastic film of Sakuragawa is considered to be a supporting synthetic membrane.

The intended use limitations in claims 3-6 and 9 are not given patentable weight because the specification does not teach how these intended uses further limit the active method steps or the structure of the recited cells or molecules. Because Sakuragawa teaches all the steps of the method, as well as the structures of the claimed cells and molecule, Sakuragawa anticipates these claims.

In any case, even if the intended use language of claims 3-6 was given patentable weight Sakuragawa would still be anticipatory for the following reasons. Amniotic epithelial cells were known prior to the time of filing to secrete the growth factor NGF. So, regardless of whether or not the method of Sakuragawa is enabled for gene therapy, the cells are deemed to deliver to the surrounding dermal cells a detectable amount of NGF in view of Uchida. Note that claims 6, 14, 15, and 19, which require an exogenous polynucleotide, recite no nexus between the polynucleotide and the delivered molecule, so there is no requirement for the delivered molecule to be encoded by the polynucleotide. Instant claims 3-6 are drawn to the method of claim 1, wherein the molecule is useful for achieving a desired effect (claim 3), and wherein the cells deliver an amount of the molecule sufficient to achieve that effect (claims 4-6).

The claims do not limit the nature of the desired effect, so it is interpreted broadly. For example, the desired effect could be interpreted as "sufficient to allow detection of the molecule." This is a reasonable interpretation inasmuch as the molecule could serve as a diagnostic marker for the presence of the cells. Uchida teaches that amniotic epithelial cells secrete detectable amounts of NGF, so absent evidence to the contrary, the method of Sakuragawa would result in delivery to skin cells of detectable amounts of NGF.

Claim 9 is drawn to the method of claim 1 wherein the cells must be capable of delivering the molecule in a nutrient-poor environment on the skin. Absent evidence to the contrary, the capacity of amniotic epithelial cells to deliver proteins is an inherent characteristic independent of whether or not the environment is nutrient-poor, so the cells of Sakuragawa are considered to meet the limitations of this claim. " See MPEP 2112.01 or In re Best, 195 USPQ 430, 433 (CCPA 1997). The office does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPAI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ2d 1922, 1923 (BPAI 1989). "When the structure recited in the reference is substantially identical to that of the claims, claimed properties or functions are presumed to be

inherent. Furthermore, every protein in an amniotic epithelial cell can be considered to be delivered to the skin merely as a consequence of administering the amniotic epithelial cell to the skin, there is no requirement for any metabolic activity such as secretion.

Claims 1-5, 7-13, 16-18, and 20 stand rejected under 35 U.S.C. 102(b) as being anticipated by Faulk et al (Lancet 1(8179): 1156-1158, 1980) as evidenced by Uchida et al (J. Neurosci. Res. 62: 585-590, 2000).

Faulk taught a method of treating burned skin by application of amniotic basement membrane comprising amniotic epithelial cells. See abstract, and page 1156, column 2, first two paragraphs. Inasmuch as the cells of Faulk are composed of molecules, Faulk teaches the delivery of molecules to skin of a patient. Regarding the elected species of molecule to be delivered, i.e. a growth factor, Uchida et al (J. Neurosci. Res. 62: 585-590, 2000) taught that amniotic epithelial cells were known prior to the time of filing to secrete the growth factor NGF. See abstract.

The intended use limitations of claims 3-5 and 9 are not given patentable weight because the specification does not teach how these intended uses further limit the active method steps or the structure of the recited cells or molecules. Because Faulk teaches all the steps of the method, as well as the structures of the claimed cells and molecule, Faulk anticipates these claims.

Claims 16-19 stand rejected under 35 U.S.C. 102(b) as being anticipated by Eming et al (Biotech. Bioeng. 52(1): 15-23, 1996).

This rejection is directed to a generic embodiment of the rejection which does not require amniotic epithelial cells and an amniotic membrane.

Eming taught a composition comprising keratinocytes genetically modified to secrete a biologically effective amount of PDGF-A, wherein the cells were attached to a silastic support. See abstract, and page 17, column 1, second paragraph under the heading "Grafting". Thus Eming anticipates the claims.

Response to Arguments

Applicant's arguments filed 11/26/04 have been fully considered but they are not persuasive.

With regard to the rejection over Sakuragawa, Applicant argues at page 8 of the response that Sakuragawa does not teach delivering a molecule to a patient by administering epithelial cells to the skin. The basis of Applicant's argument appears to be that Applicant believes that subcutaneous delivery is not delivery "to the skin". Applicant's attention is directed to detailed description paragraph 7 which indicates that the term "subcutaneously" embraces delivery to the "subcutis." Webster's Collegiate Dictionary 10th edition defines "subcutis" as "the deeper part of the dermis." Applicant appears to argue also that Sakuragawa failed to teach delivery of a molecule. This argument is unpersuasive because it lacks evidentiary or logical support. Inasmuch as the cells of Sakuragawa are composed of molecules, Sakuragawa teaches the delivery

of molecules to skin of a patient. Regarding the elected species of molecule to be delivered, i.e. a growth factor, Uchida et al (J. Neurosci. Res. 62: 585-590, 2000) taught that amniotic epithelial cells were known prior to the time of filing to secrete the growth factor NGF. See abstract. For these reasons the rejection is maintained.

With regard to the rejection over Faulk, Applicant argues at page 8 of the response that Faulk does not teach or suggest delivering a molecule to a patient by administering amniotic epithelial cells to the skin of the patient wherein said cells are capable of delivering said molecule. Applicant asserts that this is inconsistent with the allegation of the Examiner that Faulk teaches delivery of molecules to the skin of a patient inasmuch as the cells of Faulk are composed of molecules. This is unpersuasive. If the cells of Faulk are applied to the skin of a patient, then the cells themselves have been delivered to the skin of the patient. If the cells have been delivered to the skin of the patient, it follows that all of the molecules within the cells have been delivered too. Furthermore, the prior art taught that amniotic epithelial cells secrete NGF. So, absent evidence to the contrary, the cells of Faulk secreted NFG. Because the cells of Faulk were applied to the skin of a patient, and because they secrete NGF, NGF is delivered to the skin of the patient. The rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

> invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-6 and 14-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Faulk et al (Lancet 1(8179): 1156-1158, 1980), in view of Eming et al (Biotech. Bioeng. 52(1): 15-23, 1996) and Sakuragawa (US Patent 6117676, issued 9/12/00).

Faulk taught a method of treating wounded skin by application of amniotic basement membrane comprising amniotic epithelial cells. See abstract, and page 1156, column 2, first two paragraphs.

Faulk did not teach amniotic epithelial cells engineered to include an exogenous polynucleotide.

Eming taught a method of promoting growth and vascularization in a wound by delivering PDGF-A to a patient. Epithelial keratinocytes were genetically modified to express PDGF-A, and were attached to a supporting membrane and administered to the skin of an immunodeficient (athymic) patient, resulting in improved growth and vascularization in the wound. See abstract, and page 17, column 1, second paragraph under the heading "Grafting".

Sakuragawa taught that amniotic epithelial cells could be transfected by either plasmid or adenoviral vectors, and that amniotic epithelial cells do not express HLA-A, B, C and DR antigens and do not cause rejection reactions or topical inflammation even when transplanted allogeneically. See column 2, lines 9-13 and 27-39; column 3, lines 51-67; column 4, lines 1-16 and 25-35; and column 5, line 25 to column 6, line 17.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Faulk by transfecting the amniotic epithelial cells with

the vector of Eming. One would have been motivated to do so because Eming shows that delivery of PDGF-A by transfected epithelial cells attached to a membrane results in tissue regeneration. One would have selected amniotic epithelial cells because Sakuragawa teaches that these cells can be conveniently transplanted allogeneically without rejection due to the absence of cell surface HLA class II antigens, and a much diminished amount of HLA class I antigens. This would allow study of the healing process in immune-competent animals without instigation of inflammation beyond that which is ordinarily associated with wound healing. Also, Sakuragawa demonstrates that these cells can be transfected by means of viruses or plasmids, and suggests their use in therapeutic applications involving administration of the cells to skin. Finally, using cells on an amniotic membrane, as taught by Faulk, eliminates the step of applying cells to a synthetic membrane, thereby simplifying the procedure of Eming.

Thus the invention as a whole was prima facie obvious.

Claims 1-6 and 14-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Faulk et al (Lancet 1(8179): 1156-1158, 1980), in view of Eming et al (Biotech. Bioeng. 52(1): 15-23, 1996), Sakuragawa (US Patent 6117676, issued 9/12/00), and Pollock et al (US Patent 6191269, issued 2/20/2001).

The teachings of Faulk, Eming, and Sakuragawa are discussed above and can be combined to render obvious methods and compositions for delivering molecules to a patient by genetically modifying amniotic epithelial cells to produce the molecule, and administering the amniotic epithelial cells on an amniotic membrane. These references

teach the use of plasmid or adenoviral vectors for transfection of amniotic epithelial cells.

These references do not teach the use of retroviral, lentiviral, adeno-associated virus, or cosmid vectors.

Pollock taught that plasmids, cosmids, retroviral vectors, lentiviral vectors, adenoviral vectors, and adeno-associated viral vectors could be used interchangeably as expression vectors in eukaryotic cells. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). As such, it would have been obvious to substitute retroviral, lentiviral, adeno-associated virus, or cosmid vectors for the plasmid or adenoviral vectors of Sakuragawa.

Thus the invention as a whole was prima facie obvious.

Response to Arguments

Applicant's arguments filed 11/26/04 have been fully considered but they are not persuasive.

Applicant addresses the rejection of claims 1-6, and 14-19 over Faulk in view of Eming and Sakuragawa at page 9 of the response and the rejection of claims 1-6, and 14-19 over Faulk in view of Eming, Sakuragawa, and Pollock. Applicant reiterates the

arguments set forth against the rejection under 35 USC 102 over Faulk. These arguments are unpersuasive for the reasons set forth above. Applicant asserts that there is no suggestion to combine Faulk, Eming, Sakuragawa, and or Pollock, and requests that evidence for a suggestion to combine be made of record.

MPEP 2144 states that the expectation of some advantage is the strongest rationale for combining references. As stated in the rejection, one would have been motivated to modify the method of Faulk by transfecting the amniotic epithelial cells with the vector of Eming, because Eming shows that delivery of PDGF-A by transfected epithelial cells attached to a membrane results in tissue regeneration. This is a clear advantage over the method of Faulk. Further, one would have selected amniotic epithelial cells because Sakuragawa teaches that these cells can be conveniently transplanted allogeneically without rejection due to the absence of cell surface HLA class II antigens, and a much diminished amount of HLA class I antigens. This is a clear advantage over Eming. Also, as noted in the rejection, Sakuragawa demonstrates that these cells can be transfected by means of viruses or plasmids, and suggests their use in therapeutic applications involving administration of the cells to skin. Finally, using cells on an amniotic membrane, as taught by Faulk, eliminates the step of applying cells to a synthetic membrane, thereby simplifying the procedure of Eming. Applicant has directly addressed none of the reasons to combine references that were set forth in the rejection.

Regarding the Pollock reference, as stated above in the rejection, MPEP 2144.06 indicates that an express suggestion to substitute one equivalent component for another

is not necessary to render such substitution obvious, when the components in question are art-recognized equivalents. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). It would have been obvious to substitute the retroviral, lentiviral, adeno-associated virus, or cosmid vectors of Pollock for the plasmid or adenoviral vectors of Sakuragawa, because Pollock taught that plasmids, cosmids, retroviral vectors, lentiviral vectors, adenoviral vectors, and adeno-associated viral vectors could be used interchangeably as expression vectors in eukaryotic cells.

The rejections are maintained.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, John Leguyader, be reached at 571-272-0760. The official central fax number is 703-872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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DAVE TRONG NGUYEN
PRIMARY EXAMINER

Richard Schnizer, Ph.D.